doi: 10.4183/aeb.2022.97

CASE REPORT

EMPTY SELLA IN A PATIENT WITH CLINICAL AND BIOCHEMICAL DIAGNOSIS OF ACROMEGALY

N. Bestepe[1,*], C. Aydin[2], A.A. Tam[2], K. Ercan[3], R. Ersoy[2], B. Cakir[2]

[1]Ankara City Hospital, Dept. of Endocrinology and Metabolism, [2]"Yildirim Beyazit" University, Faculty of Medicine, Dept. of Endocrinology and Metabolism, [3]Ankara City Hospital, Dept. of Radiology, Ankara, Turkey

Abstract

Background. Acromegaly is an acquired disorder related to excessive production of growth hormone (GH) and insulin-like growth factor-1 (IGF-1). Empty sella (ES) is an anatomical condition of sella turcica that is partially or completely filled with cerebrospinal fluid mainly due to intrasellar herniation of subarachnoid space. Here, we describe a patient who presented with clinical and biochemical features of acromegaly and who had an ES on pituitary magnetic resonance imaging (MRI).

Case report. A 73-year-old male patient was consulted in our clinic because of the acromegalic phenotype while planning for colorectal adenocarcinoma surgery. The patient noticed gradual enlarging of his hands, feet and nose for 30 years, but never consulted to any clinician for this reason. Serum GH was 20.6 ng/mL (normal <3 ng/mL) and IGF-1 was 531 ng/mL (normal, 69–200 ng/ml). An oral glucose tolerance test showed no suppression of GH values. T1-weighted MRI revealed an ES. 18F-FDG PET/CT and Ga-DOTATADE PET/CT did not show any finding consistent with ectopic GH secretion. Growth hormone releasing hormone (GHRH) was within the normal range (<100mg/dL). He was treated with long-acting octreotide 20 mg per 28 days. At the 6th month of treatment, serum GH and IGF-1 levels were decreased to 5.45 ng/mL and 274 ng/mL, respectively.

Conclusion. The mechanism underlying the association of acromegaly and ES remains unclear. Apoplexy on existing pituitary adenoma and then formation of necrosis can proceed to ES. Since our patient did not have a history of pituitary apoplexy and we could not find any reason for secondary ES, we considered primary ES.

Keywords: acromegaly, empty sella syndrome, pituitary tumor.

INTRODUCTION

Acromegaly is characterized by progressive somatic deformity and systemic symptoms associated with excessive growth hormone (GH) production (1). The mean age at diagnosis of acromegaly ranges from 40 to 47 years, with a prevalence of 28–137 per million and an incidence of 2–11 cases / year (2). Men and women are affected equally. Due to the insidious onset and slow progression, the period between the onset of the symptoms and the diagnosis is an average of 5 years, and it is known that this period may extend up to 15 years (3). Acromegaly stems from GH-secreting pituitary tumors in approximately 95% of all cases, and most tumors are visible on magnetic resonance imaging (MRI) of the sella (4). In 5% of cases, it is caused by the ectopic secretion of growth hormone-releasing hormone (GHRH), which is responsible for pituitary hyperplasia (5).

The empty sella (ES) is characterized by herniation of the subarachnoid space within the sella, usually associated with varying degrees of flattening of the pituitary gland. It is the radiological finding of a flattened pituitary in the sellar cavity filled with cerebrospinal fluid (6,7). ES may occur due to the inherent weakness of the diaphragm sella and/or the increase in intracranial pressure promoting herniation of the arachnoid membrane into the pituitary pit. This is referred to as primary ES (8). On the other hand, when ES is seen after surgery, irradiation, or medical treatment of pituitary adenoma, it is defined as secondary (9). Incidental primary ES has increased with the widespread use of conventional imaging methods such as computed tomography (CT) and MRI. ES is a common finding and according to the results of autopsy and radiological examinations, the prevalence in the population varies between 5.5% and 35%. The female-to-male ratio was reported as 4:1 (7,10-12). Hyperprolactinemia or partial to total hypopituitarism can be detected in approximately 50% of patients (13-15). The most common hormone deficiency in ES is

*Correspondence to: Nagihan Bestepe MD, Ankara City Hospital, Dept. of Endocrinology and Metabolism, Ankara, Turkey, E-mail: nagihanbestepe@gmail.com

growth hormone (GH) deficiency, affecting 35 to 61% of patients (16-18). Pituitary hyperfunction is rarely seen in ES and acromegaly is perhaps the least common finding (19-21).

The cause of an enlarged ES may be a congenital incomplete sellar diaphragm with or without change in cerebrospinal fluid dynamics, previous pituitary gland hypertrophy, or pituitary tumor necrosis. Increased intracranial pressure will cause sellar enlargement and hence void in some patients. Data from the literature indicate that enlarged ES and its associated findings are in most cases caused by spontaneous necrosis of a previous pituitary adenoma. This theory explains the common presence of pituitary insufficiency, pituitary hypersecretion, and visual field defects in patients with ES. An empty enlarged sella is a stage in the spontaneous course of some pituitary adenomas, and the associated findings that make up the ES can sometimes be part of the clinical presentation of pituitary adenomas.

In this case report, we present a patient with clinical and biochemical features of acromegaly and ES on pituitary MRI.

CASE PRESENTATION

A 73-year-old male patient was consulted to our clinic for acromegaly phenotype while being evaluated for a newly diagnosed colorectal adenocarcinoma that has metastasized to the liver. The patient noticed gradual enlarging of his hands, feet, lips, and nose for 30 years, but never consulted to any clinician for this reason. He complained of weakness and fatigue. The patient had an additional diagnosis of hypertension and type 2 diabetes mellitus. He did not report any family history of endocrine disorders. On physical examination, he had a typical acromegaly phenotype with coarse facial features, enlarged nose, macrognathia, macroglossia, thyromegaly with no palpable nodules, acral enlargement of hands with broad fingers. Blood pressure was 145/88 mmHg. He was using nifedipine 60 mg/day, candesartan 16 mg/day and metformin 2 g/day. Visual field defect was not detected.

Laboratory data showed a fasting blood glucose of 128 mg/dL and an HbA1c of 7.2%. Serum GH was 20.6 ng/mL (normal <3 ng/mL) and insulin-like growth factor-1 (IGF-1) was 531 ng/mL (normal, 64-188 ng/mL). Oral glucose tolerance test (OGTT) showed no suppression of GH values with the nadir GH level of 5.6 ng/mL. Serum levels of prolactin (PRL), adrenocorticotropic hormone (ACTH), cortisol (CS), thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were normal. Relevant laboratory data are shown in Table 1.

Sella contrast-enhanced MRI was performed for tumor localization and T1 and T2 - weighted images revealed ES and no adenoma (Fig. 1A, B).

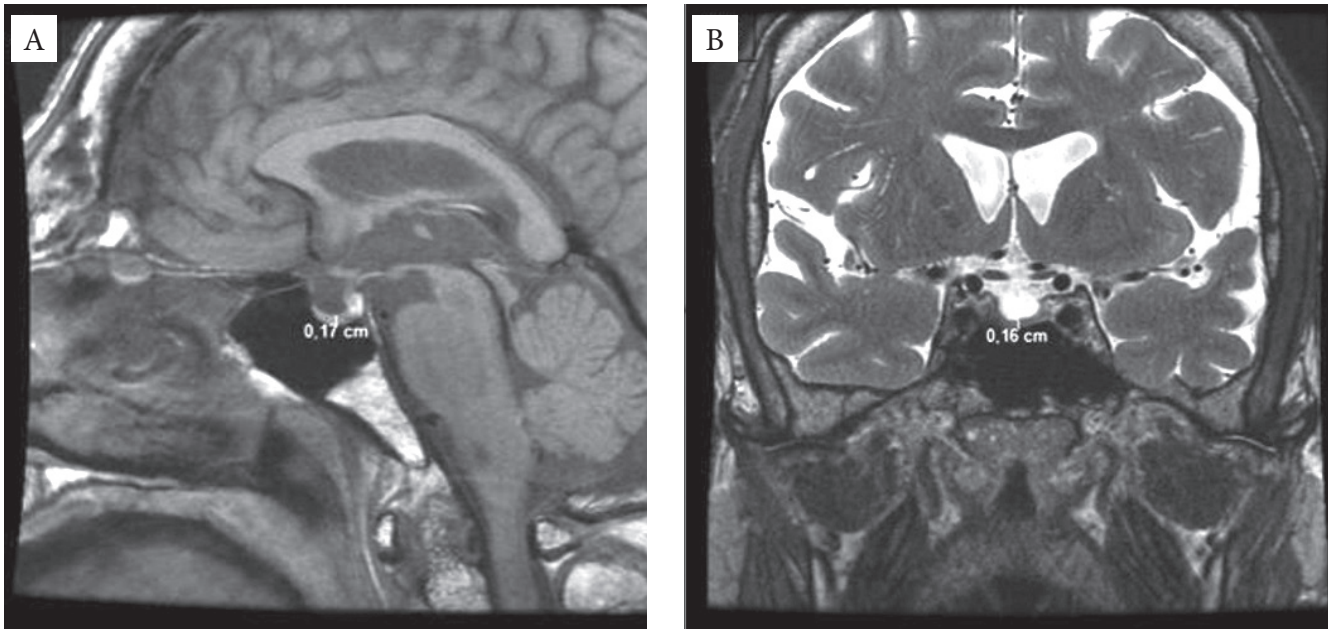

Figure 1. MRI images of the pituitary showing ESS. Sagittal (A) T1 weighted and coronal (B) T2-weighted MR image demonstrate a presence of empty sella. Sagittal view of pituitary MRI shows a flattened pituitary gland and CSF space herniated into the sellar turcica (pituitary gland height 0.17 cm). Coronal view of pituitary MRI shows the pituitary fossa, which is largely empty of tissue, replaced by CSF (pituitary gland height 0.16 cm). MRI = magnetic resonance imaging, ESS = empty sella syndrome, CSF = cerebrospinal fluid.

Subsequently, contrast-enhanced CT imaging of the chest, abdomen, and pelvis, 18F-FDG PET-CT, as well as Ga-DOTATADE PET/CT were performed to search for a possible ectopic source of GH secretion. No evidence of an ectopic GH or GHRH secreting tumor was detected. Also, serum GHRH level was <100 mg / dL (normal range <100 mg/dL).

The patient was referred to our clinic for acromegaly treatment after surgery for colorectal adenocarcinoma and initiation of chemotherapy. Long-term medical therapy *versus* exploratory pituitary surgery were discussed with the patient and he opted for a long-term medical treatment. Long-acting octreotide 20 mg per 28 days was initiated. At the 6th month of treatment, serum GH and IGF-1 levels were decreased to 5.45 ng/mL and 274 ng/mL, respectively. The patient's symptoms improved significantly, and his IGF-1 level returned to normal level in the 9 months. He is being followed for acromegaly with medical treatment for 2 years and his IGF-1 levels are within normal limits.

DISCUSSION

Acromegaly is characterized by uncontrolled excessive secretion of GH and GH-mediated production of IGF-1 from the liver. Due to its slow progression and insidious nature, diagnosis is often delayed. Acromegaly causes a wide variety of clinical disorders including cardiovascular, respiratory, rheumatologic, and metabolic morbidities. In addition, if left untreated it is associated with decreased life expectancy (22, 23). The IGF-1 level should be checked first in a patient with clinical suspicion of acromegaly since it is high in almost all acromegaly patients (24). The clinical diagnosis is confirmed biochemically by an unsuppressed serum GH concentration following an OGTT. A nadir serum GH level of <1 ng / mL during 75 g OGTT excludes acromegaly diagnosis. With the use of very sensitive tests nowadays, it has recently been suggested that this threshold should be reduced to 0.3 ng / mL (22, 25).

Table 1. Hormonal values of the patient at admission and values after 9 months of long-acting octreotide treatment

Hormone (units)	Patient's value at admission	Patient's value at 9 months of treatment
GH (0.05-3.0 ng/mL)	20.6	10.5
IGF-1 (64-188 ng/mL)	531	183
TSH (0.55-4.78 mU/L)	1.82	1.64
fT3 (2.3-4.2 ng/L)	2.67	2.51
fT4 (0.89-1.76 ng/dL)	1.05	1.12
LH (3.1-34.6 U/L)	3.5	4.1
FSH (3.1-34.6 U/L)	7.7	8.6
Testosterone (86-783 ng/dL)	260	274
Prolactin (2.1-17.7 µg/L)	10.8	14.1
ACTH (<46 pg/mL)	19.5	16.1
Cortisol (5.2-22.4 µg/dL)	18.2	14.2
GHRH (<100 mg/dL)	<100	

GH: growth hormone, IGF-1: insulin-like growth factor-1, TSH: thyroid-stimulating hormone, fT3: free triiodothyronine, fT4: free thyroxine, FSH: follicle-stimulating hormone, LH: luteinizing hormone, GHRH: growth hormone releasing hormone.

After biochemical diagnosis of acromegaly, the source of excess GH secretion must be determined. Pituitary MRI is the first step to identify the possible source because in more than 95% of cases, acromegaly is caused by excessive GH secretion from an adenoma originating from the somatotroph cells of the pituitary gland (4). In 5% of the cases, excessive GHRH secretion from hypothalamic or neuroendocrine tumors causes somatotroph hyperplasia and acromegaly development (5). GH-producing adenomas of the pituitary gland are usually larger than 10 mm and can be easily identified on MRI, microadenomas are rare (26, 27). Therefore, if an adenoma cannot be detected on pituitary MRI, a contrast-enhanced CT scan of the chest, abdomen, and pelvis should be performed to look for the source of ectopic GH / GHRH.

Coexistence of acromegaly and ES was rarely reported in patients with previous pituitary radiation and / or surgery, but its association with primary ES was observed even more rarely (21, 28). In our case, there was an ES image without a prominent adenoma on MRI. The relationship between acromegaly and ES in the literature is generally in the form of case reports, and the first cases were described in the 1980s. Molitch *et al*. reported two patients with an ES who presented with active acromegaly (21). Bjerre *et al*. evaluated 23 patients with acromegaly untreated for 2-13 years and revealed ES on CT scans of 11 patients (28). In another study including 36 acromegalic patients, 3 cases had ES were described (29). Gallardo *et al*. described only three patients with acromegaly in their retrospective study involving 76 patients with ES (30).

Data from the literature indicate that enlarged ES and associated findings are mostly due to spontaneous necrosis of a previous pituitary adenoma. Pituitary apoplexy is considered as one of the main causes of ES in patients with pituitary tumors (31). This theory provides an explanation for high frequency of pituitary insufficiency, pituitary hypersecretion, and visual field defects in patients with ES as well as for the

presence of an empty enlarged sella in some patients with non-traumatic cerebrospinal fluid rhinorrhea and benign intracranial hypertension (32). Thus, an empty enlarged sella may be a stage in the spontaneous course of some pituitary adenomas. In Bjerre's series, there were findings suggesting that 6 of 11 patients with ES and 2 intracellar cysts had pituitary apoplexy (28). In another case report, the spontaneous evolution of a GH-producing pituitary adenoma resulted in an ES without signs of pituitary apoplexy (33). When we questioned our patient in detail, he didn't describe any symptoms of pituitary apoplexy. Therefore, bleeding into adenoma and subsequent tissue shrinkage could not fully explain our case, but we do not know whether ES developed without any clinical symptom or sign of apoplexy.

While autoremission of acromegaly after pituitary infarction or hemorrhage has been described, it is uncommon for a GH secreting pituitary adenoma to evade visualization on pituitary MRI, much less for an ES alone to be present (34, 35). In cases where only an ES is visualized, ectopic acromegaly should be considered, though it is responsible for less than 5 % of cases. Therefore, we focused to search for a lesion that could cause ectopic acromegaly in our patient. Most ectopic acromegaly results from neuroendocrine GHRH-secreting tumors. However, in our patient, we excluded an ectopic GHRH-secreting neuroendocrine tumor by low GHRH and lack of any ectopic focus in contrast-enhanced CT imaging of the chest, abdomen, and pelvis, Ga-DOTATADE PET/CT, 18 F-fluorodeoxyglucose positron emission tomography-CT (18 FDG PET-CT).

Acromegaly secondary to a very small pituitary microadenoma that cannot be visualized on pituitary MRI is rare. In the literature, there are very few patients who have negative pituitary imaging and have adenomas detected in pituitary examination. Daud *et al*. reported surgical exploration of a 9-mm adenoma in an acromegalic patient with no imaging evidence of a pituitary adenoma with contrast-enhanced MRI (36). Doppman *et al*. described three patients with acromegaly whose pituitary adenoma was not detected on MRI and was later discovered on pituitary exploration. Resected adenoma sizes were reported as 6-10 mm (37). Of note, in two patients, noncontrast MRI which may not be a sensitive imaging for microadenomas was performed. Lonser *et al*. reported a case series of six acromegalic patients without imaging evidence of pituitary adenoma on conventional contrast enhanced MRI. A post-contrast fine-cut VIBE MRI sequence was performed in three patients in the series and revealed a 4 mm pituitary adenoma in only one patient, but no evidence of adenoma in two patients. However, 5-6.7 mm pituitary microadenomas could be detected in all cases during surgical exploration and histological analysis of the resected lesions confirmed GH-secreting adenomas (38).

The mechanism underlying the relationship between acromegaly and ES remains unclear. Our patient reminds us of those patients whose diagnosis is delayed and who have not been treated for a long time may present with accompanying ES and active acromegaly signs and symptoms. It can be hypothesized that our patient had a pituitary infarction that resulted in an ES and this possible infarction may not have completely removed the hyperfunctional tissue, but we could not visualize this functional sellar lesion. If the patient had accepted pituitary exploration, perhaps a pituitary microadenoma could be detected. On the other hand, he had no history of pituitary apoplexy and since we could not find any evidence of secondary ES, we suggested that he had primary ES.

Conflict of interest

The authors declare that they have no conflict of interest.

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